

EXHIBIT 1



US006827901B2

(12) **United States Patent**
Copeland et al.

(10) Patent No.: **US 6,827,901 B2**

(45) Date of Patent: **Dec. 7, 2004**

(54) **AUTOMATED BIOLOGICAL REACTION APPARATUS**

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(21) Appl. No.: **10/137,169**

(22) Filed: **May 2, 2002**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/931,513, filed on Aug. 16, 2001, which is a continuation of application No. 09/452,309, filed on Dec. 1, 1999, now Pat. No. 6,352,861, which is a continuation of application No. 08/906,678, filed on Aug. 5, 1997, now abandoned, which is a continuation of application No. 08/479,415, filed on Jun. 6, 1995, now Pat. No. 5,654,200, which is a division of application No. 08/352,966, filed on Dec. 9, 1994, now Pat. No. 5,595,707, which is a continuation of application No. 07/924,052, filed on Aug. 31, 1992, now abandoned, which is a continuation-in-part of application No. 07/488,601, filed on Mar. 2, 1990, now abandoned.

(51) Int. Cl.⁷ **G01N 35/00**

(52) U.S. Cl. **422/64; 422/62; 422/67; 436/43; 436/45; 436/46; 436/54; 436/55**

(58) Field of Search **436/43, 45, 46, 436/48, 49, 54-55; 422/62, 64, 67**

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,219,416 A	11/1965	Natelson	23/253
3,398,935 A	8/1968	Livesey et al.	259/18
3,482,082 A	12/1969	Isreeli	
3,574,064 A	4/1971	Binnings et al.	195/127
3,644,715 A	2/1972	Holderith	

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP	0 285 851	10/1988
EP	0290018	11/1988

(List continued on next page.)

OTHER PUBLICATIONS

E. Stark et al., "An automated device for immunocytochemistry," *Journal of Immunological Methods* 107:89-92 (1988).

(List continued on next page.)

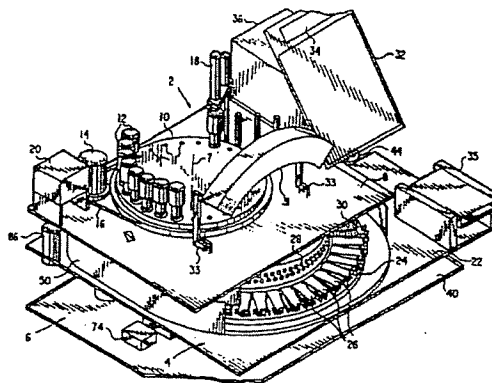
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(57) **ABSTRACT**

An automated immunostaining apparatus having a reagent application zone and a reagent supply zone. The apparatus has a carousel slide support supporting a plurality of slide supports thereon, and drive means engaging the carousel slide support for consecutively positioning each of a plurality of slide supports in the reagent application zone. The apparatus also has a carousel reagent support having a plurality of reagent container supports thereon, and drive means engaging the carousel for rotating the carousel and positioning a preselected reagent container support in the reagent supply zone. The apparatus also has a reagent delivery actuator means positioned for engaging a reagent container positioned on a container support.

45 Claims, 37 Drawing Sheets



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U.S. PATENT DOCUMENTS

3,660,638 A	5/1972	Oberli	
3,772,154 A	11/1973	Isenberg et al.	
3,831,006 A	8/1974	Chaffin, III et al.	
3,853,092 A	12/1974	Amos et al.	118/56
3,854,703 A	12/1974	Gibbs et al.	259/11
3,909,203 A	9/1975	Young et al.	
3,916,157 A	10/1975	Roulette et al.	
4,013,038 A	3/1977	Rogers et al.	118/5
4,066,412 A	1/1978	Johnson et al.	
4,092,952 A	6/1978	Wilkie et al.	118/58
4,113,437 A	9/1978	Duff et al.	
4,133,642 A	1/1979	Nosaka et al.	
4,135,883 A	1/1979	McNeil et al.	
4,159,875 A	7/1979	Hauser	
4,163,643 A	8/1979	Hunter et al.	
4,200,056 A	4/1980	Johnson	118/401
4,200,607 A	4/1980	Suzuki	
4,245,967 A	1/1981	Busselet	417/510
4,281,387 A	7/1981	Kraft et al.	
RE30,730 E	9/1981	Duff	422/64
4,298,571 A	11/1981	DiFulvio et al.	422/65
4,338,279 A	7/1982	Orimo et al.	
4,346,056 A	8/1982	Sakurada	422/64
4,371,498 A	2/1983	Scordato et al.	
4,406,547 A	9/1983	Aihara	356/414
4,447,395 A	5/1984	Englar et al.	422/68
4,455,280 A	6/1984	Shinohara et al.	422/63
4,517,160 A	5/1985	Galle et al.	
4,528,159 A	7/1985	Liston	422/65
4,558,946 A	12/1985	Galle et al.	
4,567,748 A	2/1986	Klass et al.	
4,585,622 A	4/1986	Bowe et al.	
4,634,576 A	1/1987	Galle et al.	
4,643,879 A	2/1987	Hanaway	
4,647,432 A	3/1987	Wakatake	
4,656,006 A	4/1987	Assmann et al.	
4,664,526 A	5/1987	Scheffler et al.	366/106
4,675,299 A	6/1987	Witty et al.	
4,678,752 A	7/1987	Thorne et al.	
4,678,894 A	7/1987	Shafer	
4,681,741 A	7/1987	Hanaway	422/100
4,683,120 A	7/1987	Meserol et al.	
4,692,308 A	9/1987	Riley et al.	
4,708,886 A	11/1987	Nelson	422/72
4,719,087 A	1/1988	Hanaway	
4,727,033 A	2/1988	Hijikata et al.	
4,729,661 A	3/1988	Bell	
4,764,342 A	8/1988	Kelln et al.	422/72
4,774,055 A	9/1988	Wakatake et al.	422/64
4,781,891 A	11/1988	Galle et al.	422/64
4,795,613 A	1/1989	Azuma et al.	
4,795,710 A	1/1989	Muszak et al.	435/287
4,808,380 A	2/1989	Minckane	
4,815,978 A	3/1989	Mazza et al.	435/4
4,824,641 A	4/1989	Williams	
4,844,868 A	7/1989	Rokugawa	422/64
4,844,887 A	7/1989	Galle et al.	
4,847,208 A	7/1989	Bogen	
4,849,177 A	7/1989	Jordan	
4,855,109 A	8/1989	Muraishi et al.	
4,855,110 A	8/1989	Marker et al.	
4,865,811 A	9/1989	Newton et al.	
4,900,513 A	2/1990	Barker et al.	
4,919,887 A	4/1990	Wakatake	422/67
4,933,147 A	6/1990	Hollar et al.	
4,935,875 A	6/1990	Shah et al.	
4,943,415 A	7/1990	Przybylowicz et al.	
4,961,906 A	10/1990	Andersen et al.	
4,965,049 A	10/1990	Lillig et al.	422/68.1
4,985,206 A	1/1991	Bowman et al.	
4,988,482 A	1/1991	Weston	
5,031,797 A	7/1991	Boris et al.	
5,051,238 A	9/1991	Umetsu et al.	
5,059,393 A	10/1991	Quenin et al.	
5,073,504 A	12/1991	Bogen	
5,075,079 A	12/1991	Kerr et al.	
5,081,038 A	1/1992	Sugaya et al.	
5,102,624 A	4/1992	Muraishi	
5,106,583 A	4/1992	Raysberg et al.	
5,107,422 A	4/1992	Kamenitsky et al.	382/133
5,122,342 A	6/1992	McCulloch et al.	
5,180,606 A	1/1993	Stokes et al.	
5,229,074 A	7/1993	Heath et al.	
5,232,664 A	8/1993	Krawzak et al.	
5,250,262 A	10/1993	Heidt et al.	
5,311,426 A	5/1994	Donohue et al.	
5,316,452 A	5/1994	Bogen et al.	
5,316,728 A	5/1994	Hayashi et al.	
5,350,697 A	9/1994	Swope et al.	
5,355,695 A	10/1994	Kawaguchi et al.	
5,418,138 A	5/1995	Miller et al.	
5,424,036 A	6/1995	Ushikubo	
5,425,918 A	6/1995	Healey et al.	
5,439,645 A	8/1995	Saralegui et al.	
5,439,649 A	8/1995	Tseing et al.	
5,645,114 A	7/1997	Bogen et al.	
5,646,046 A	7/1997	Fischer et al.	
5,654,200 A	8/1997	Copeland et al.	
5,656,493 A	8/1997	Mullis et al.	
5,947,167 A	9/1999	Bogen et al.	
6,193,933 B1	2/2001	Sasaki et al.	

FOREIGN PATENT DOCUMENTS

FR	2239167	7/1973
FR	2258122	6/1982
GB	2216259	10/1989
JP	55107957	8/1980
JP	61076122	10/1987
JP	6114064	1/1988
JP	61190061	2/1988
JP	61205089	3/1988
JP	61242989	4/1988
JP	61275282	6/1988
JP	62202748	2/1989
JP	63082232	10/1989
JP	63144871	12/1999
WO	8503571	8/1985
WO	8700086	1/1987
WO	8802865	4/1988
WO	WO 88/02866	4/1988
WO	WO 89/01616	2/1989

OTHER PUBLICATIONS

Saiki et al., "Enzymatic Amplification of β -Globin Genomic Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anemia," *Science*, 230:1350-1353, Dec. 20, 1985.

Innis et al., "DNA sequencing with *Thermus aquaticus* DNA polymerase and direct sequencing of polymerase chain reaction-amplified DNA," *Proc. Natl. Acad. Sci. USA*, 85:9436-9440, Dec. 1988.

Lindeman et al., "Evaluation of the automation of immunoenzymatic procedures in a routine histo/cytopathological laboratory," *Histopathology*, 6:739-746, 1982.

Catalog, "Fisher 86," Allied Fisher Scientific, pp. 93-99.

Driscoll et al., "Discrete Automated Chemistry System with Tableted Reagents," *Clin. Chem.*, 29/9, pp. 1609-1615 (1983).

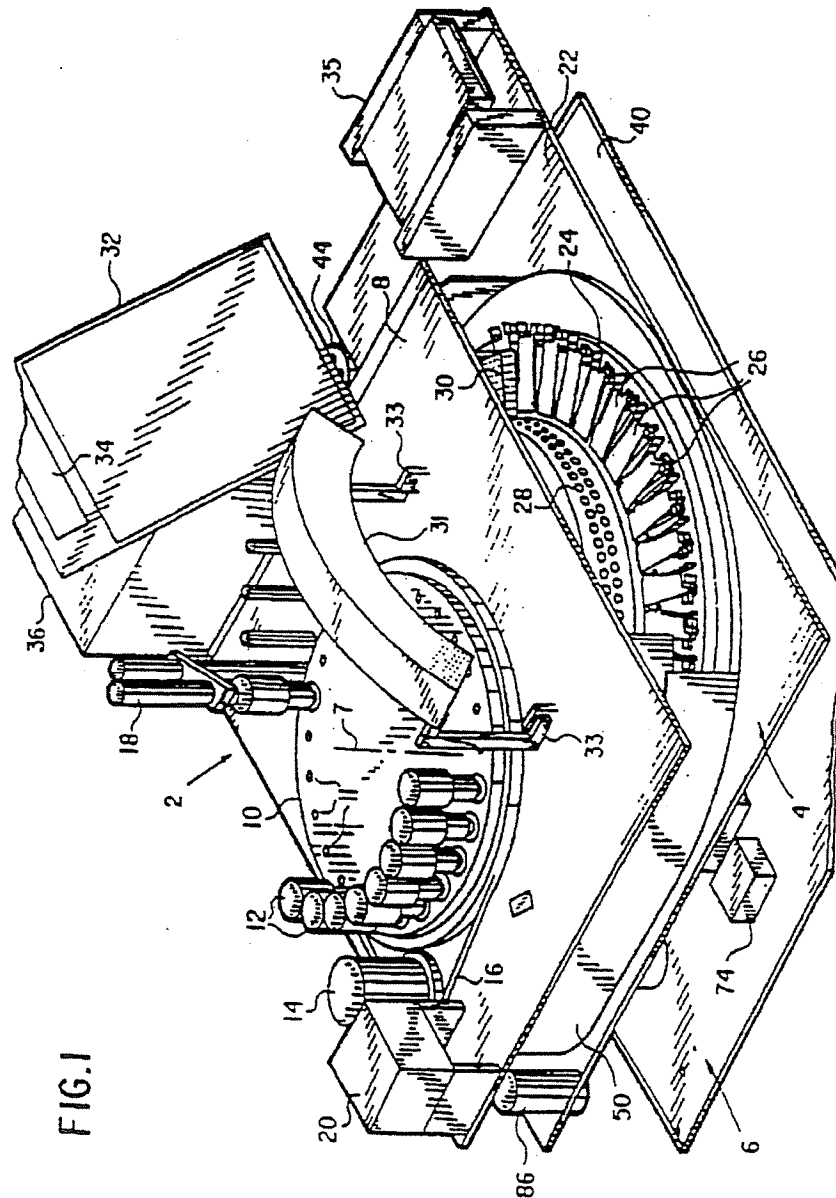
* cited by examiner

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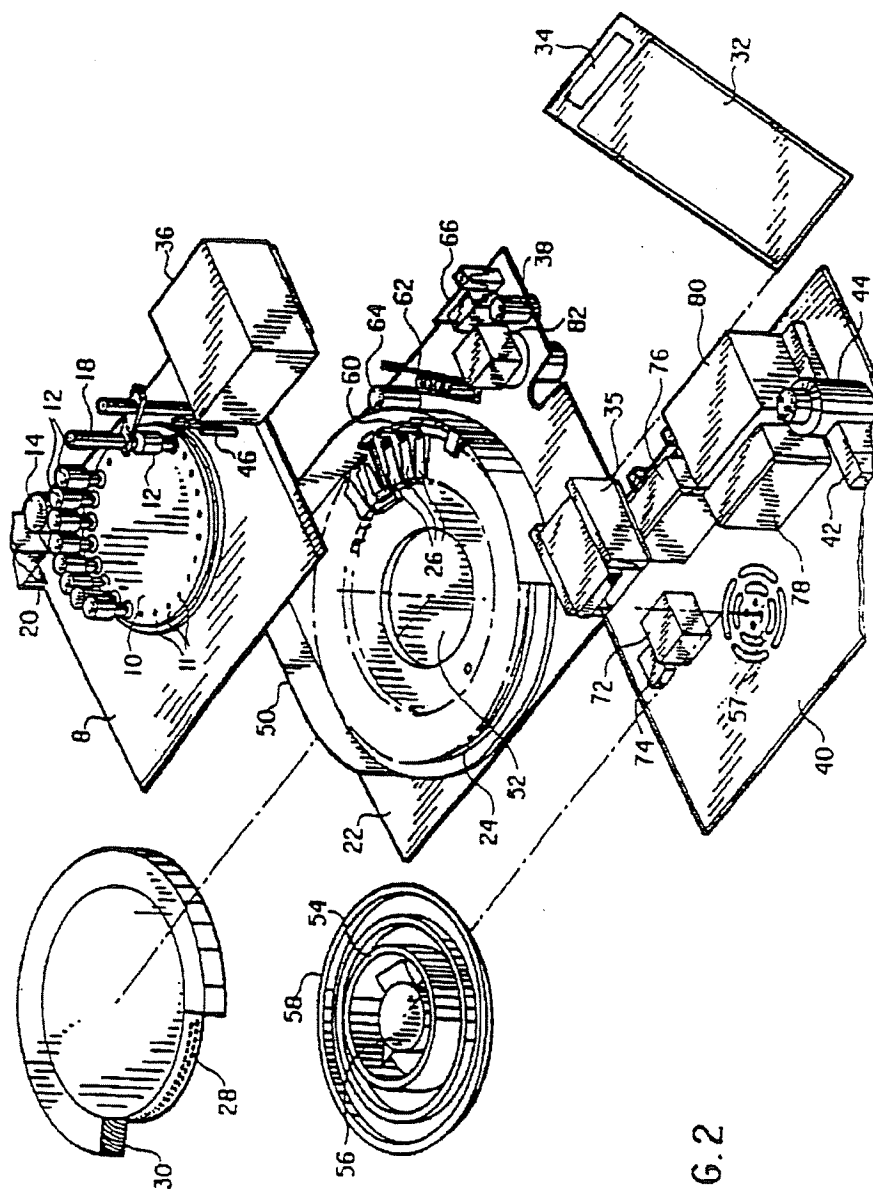


FIG. 2

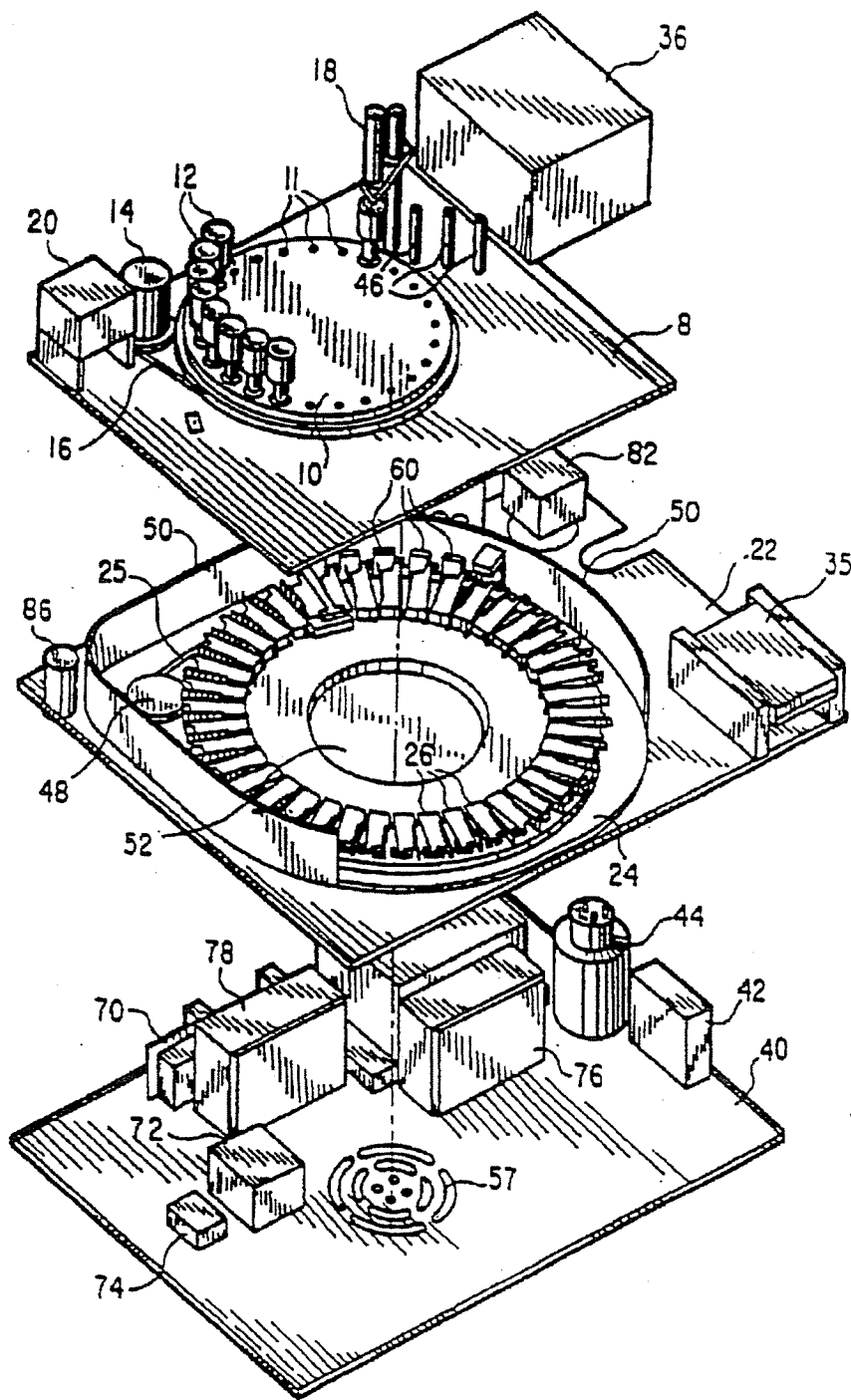
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FIG. 3



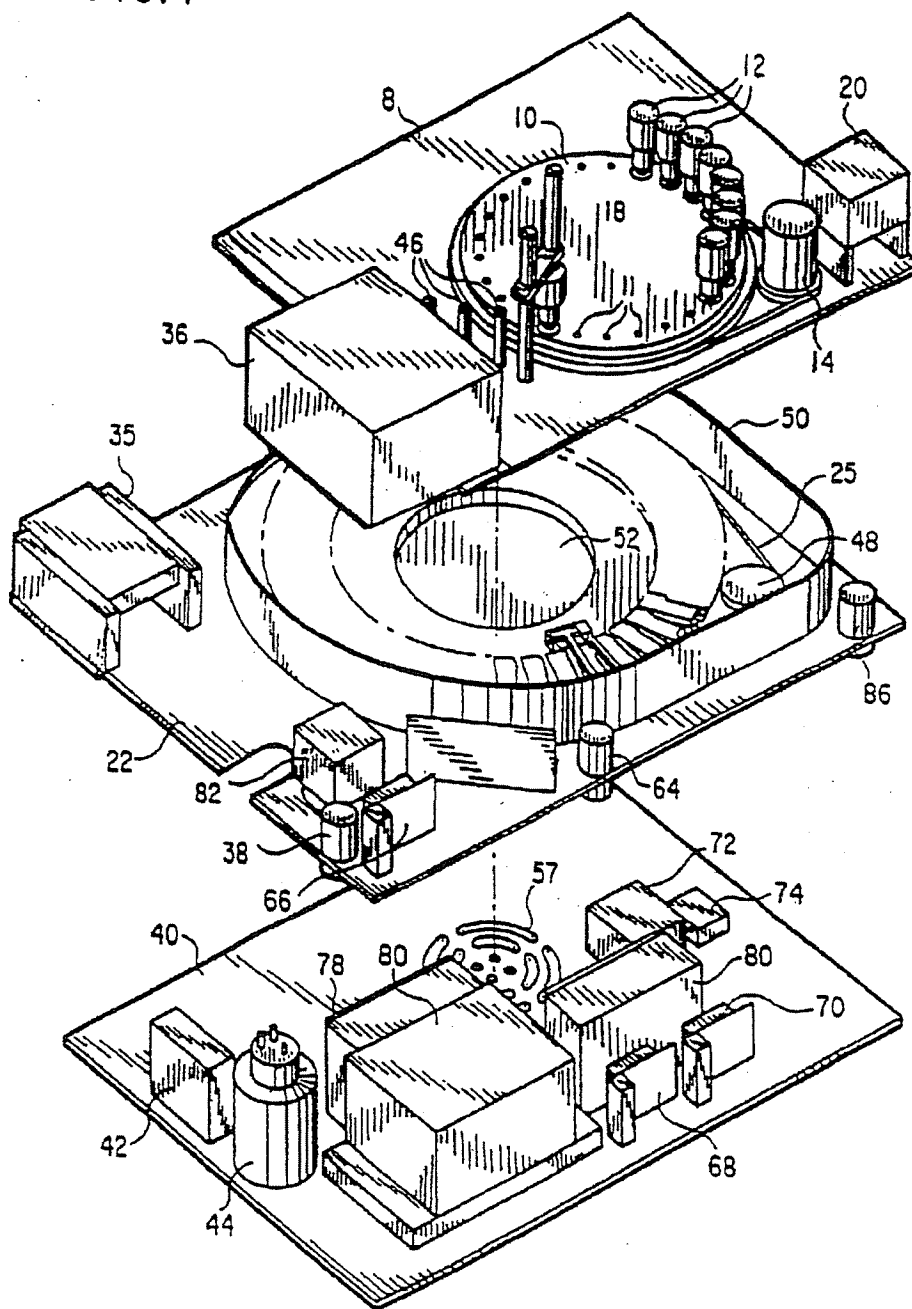
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FIG. 4



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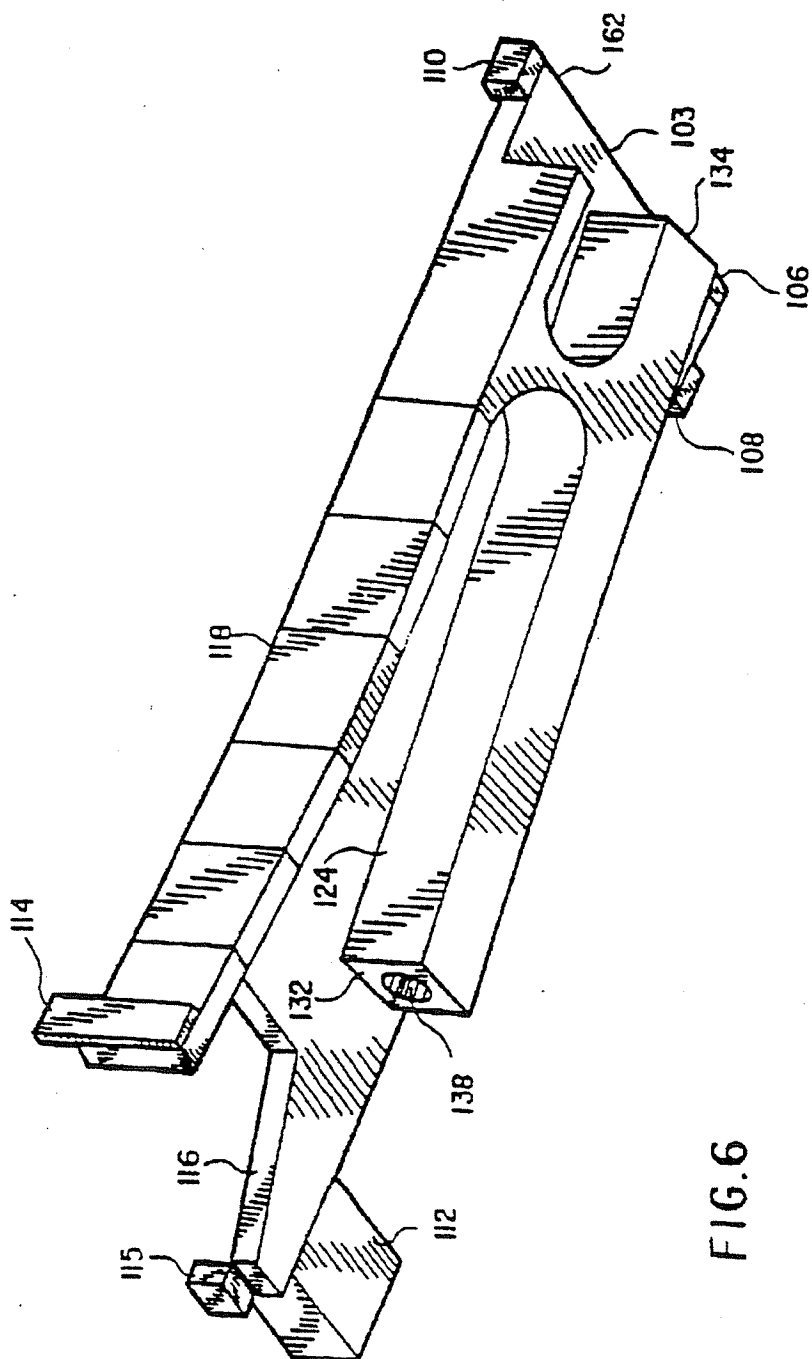
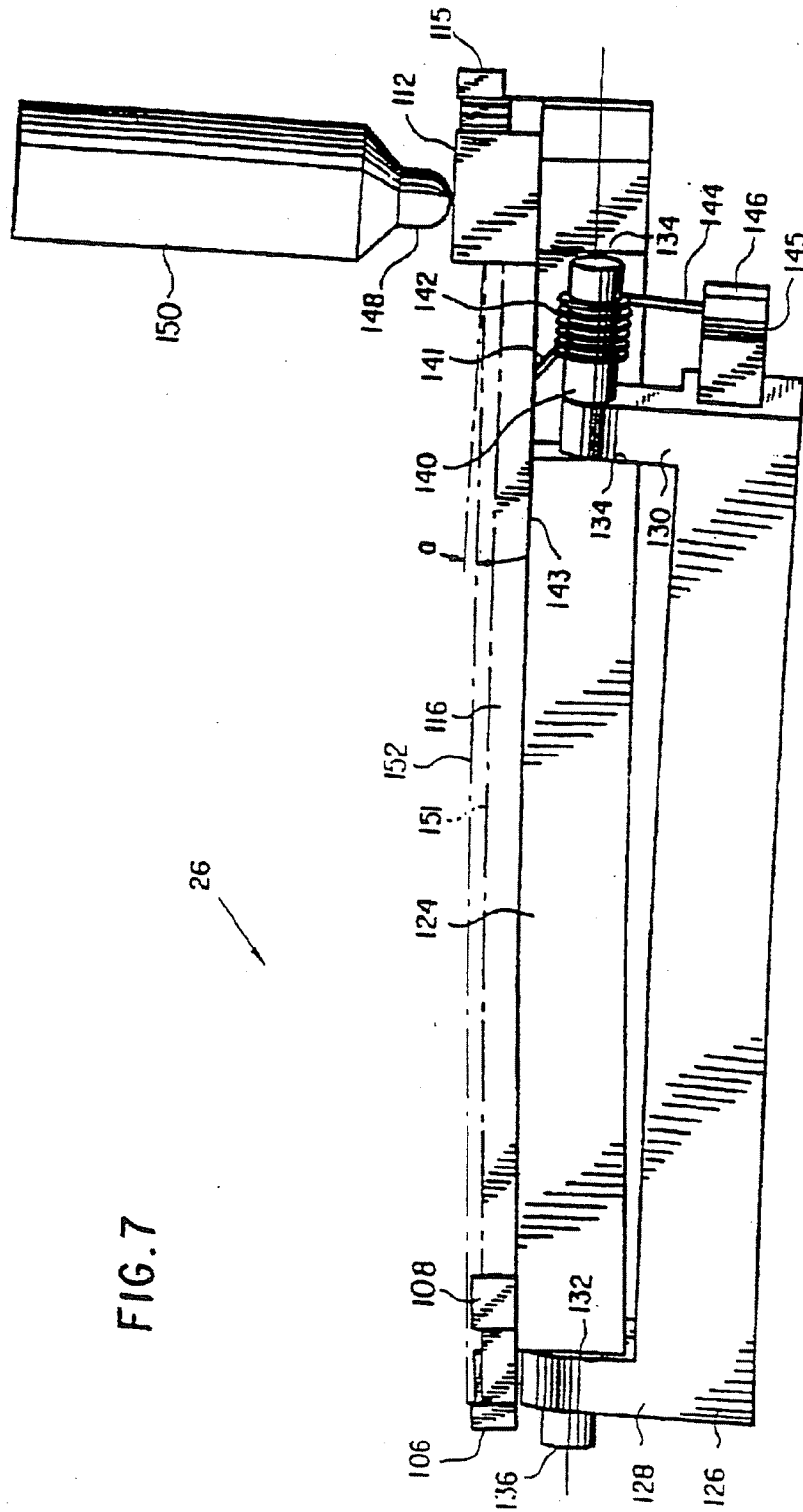


FIG. 6

FIG. 7



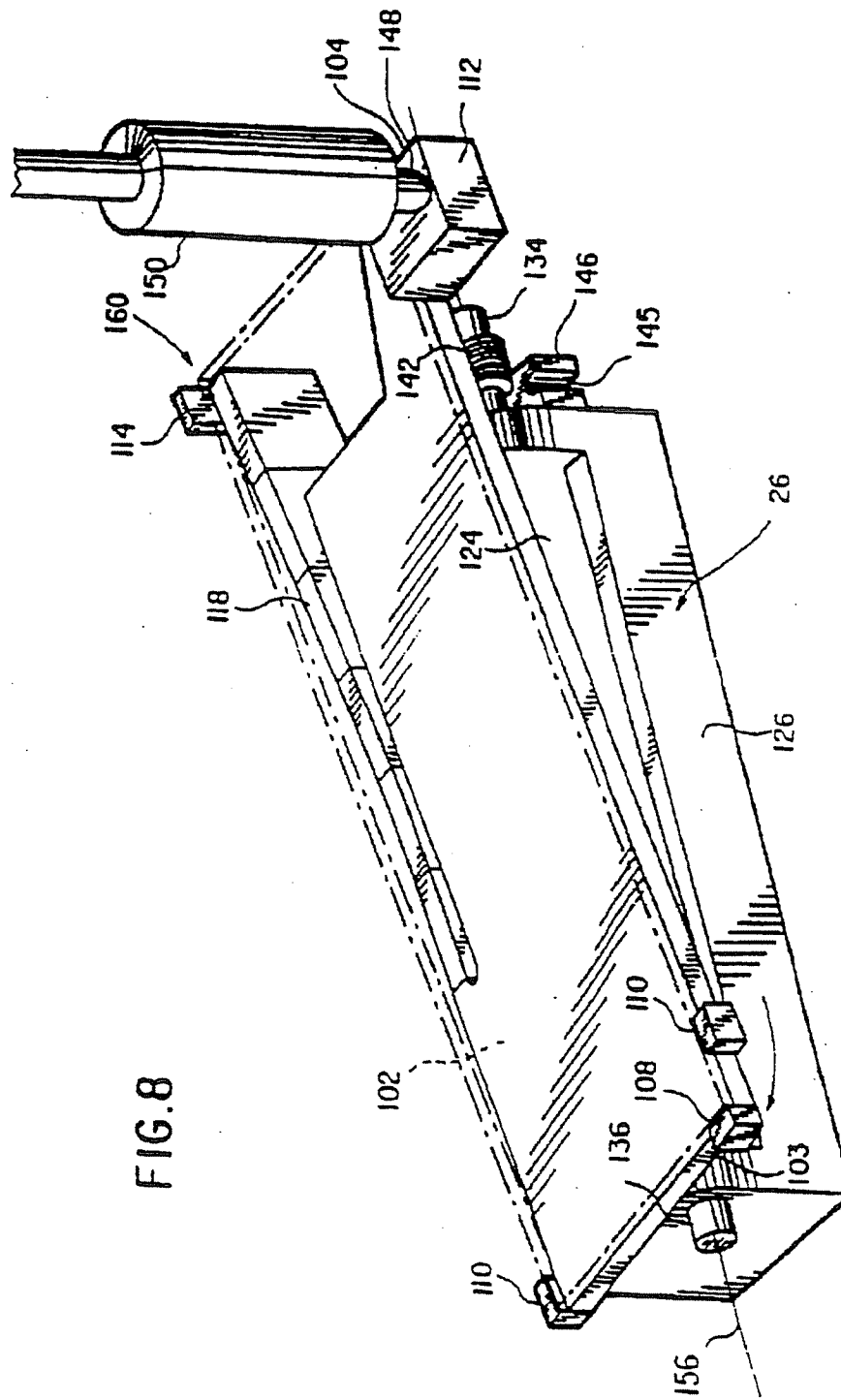
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FIG. 8



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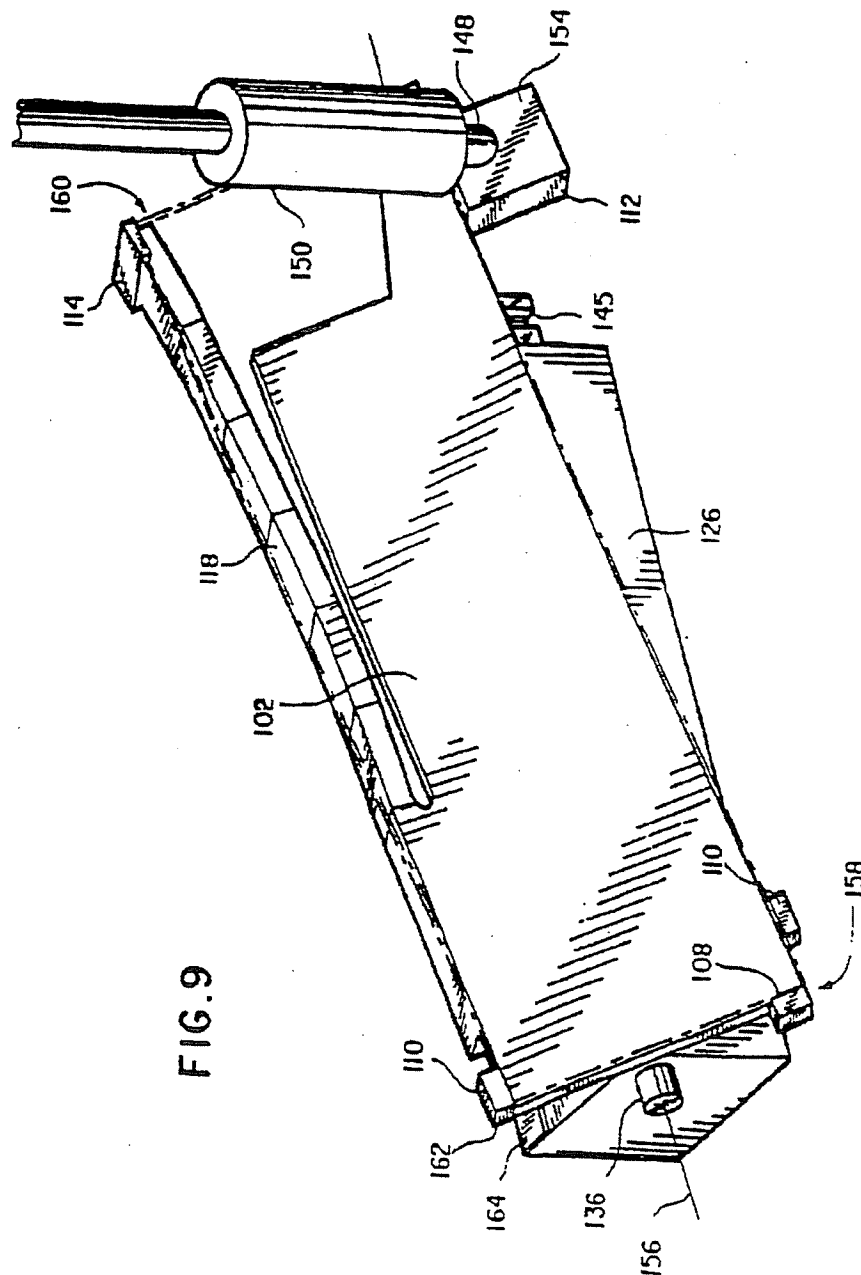
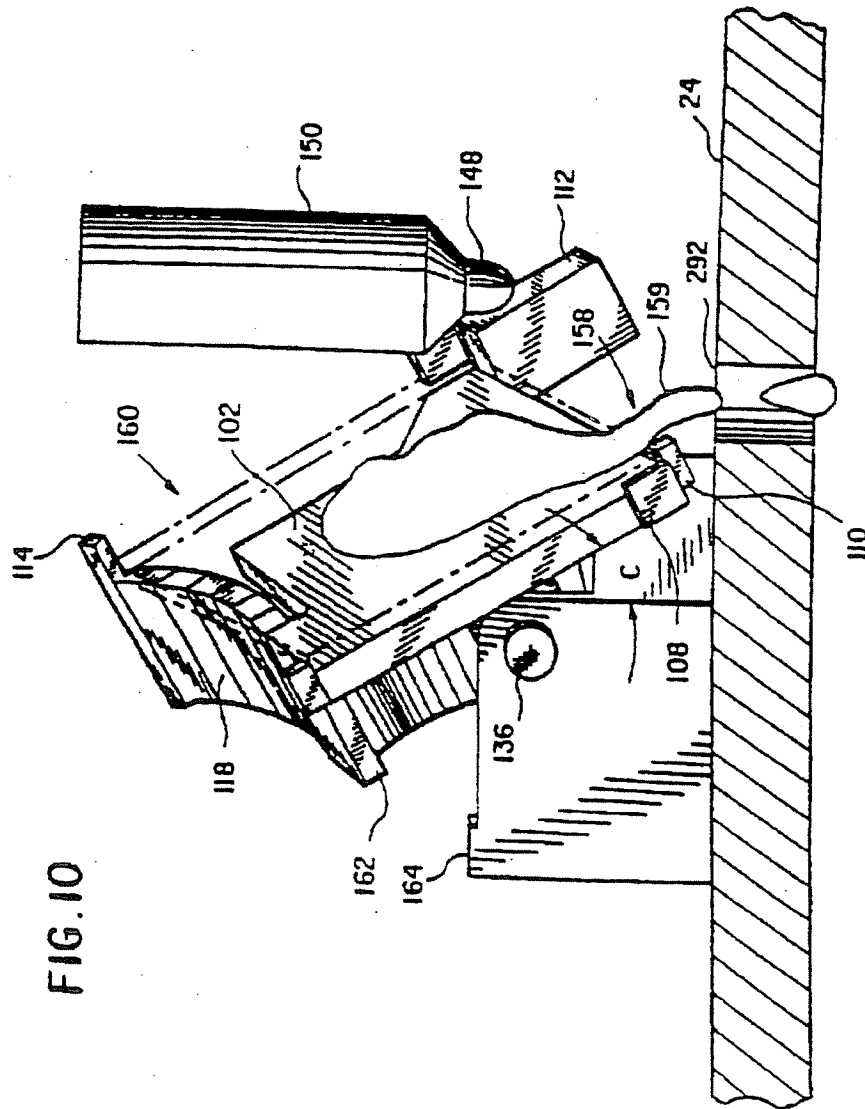


FIG. 10

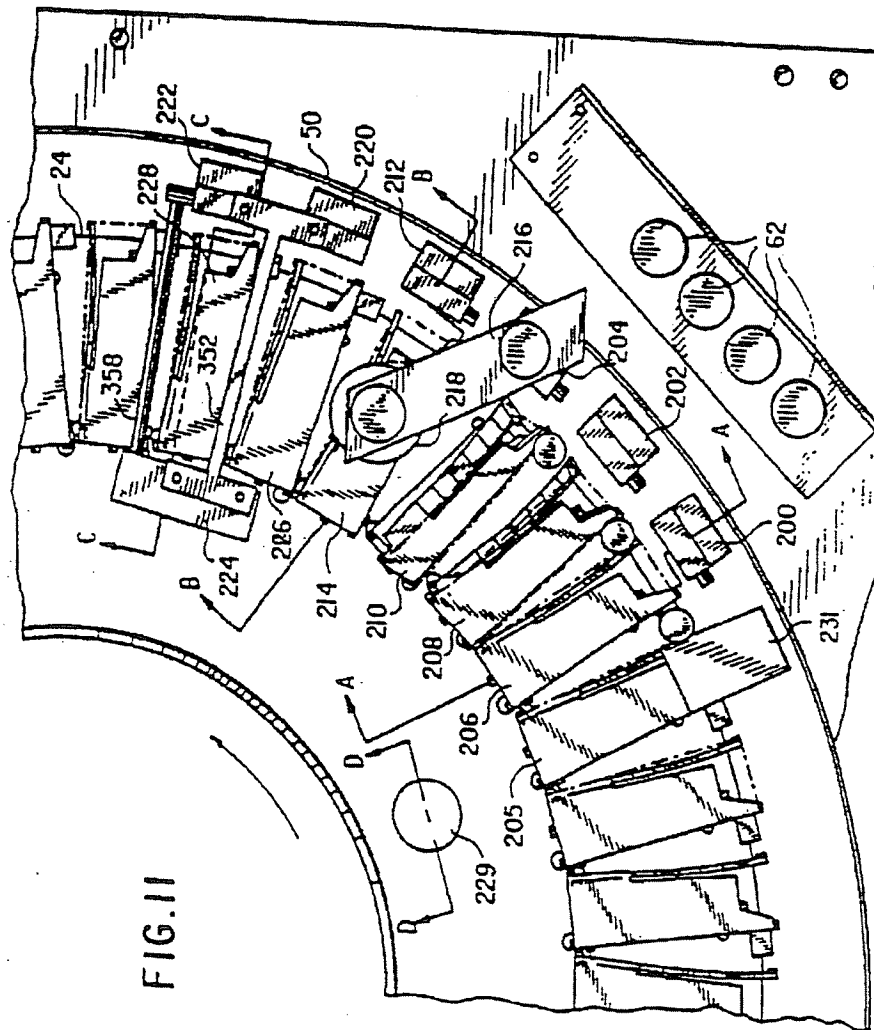


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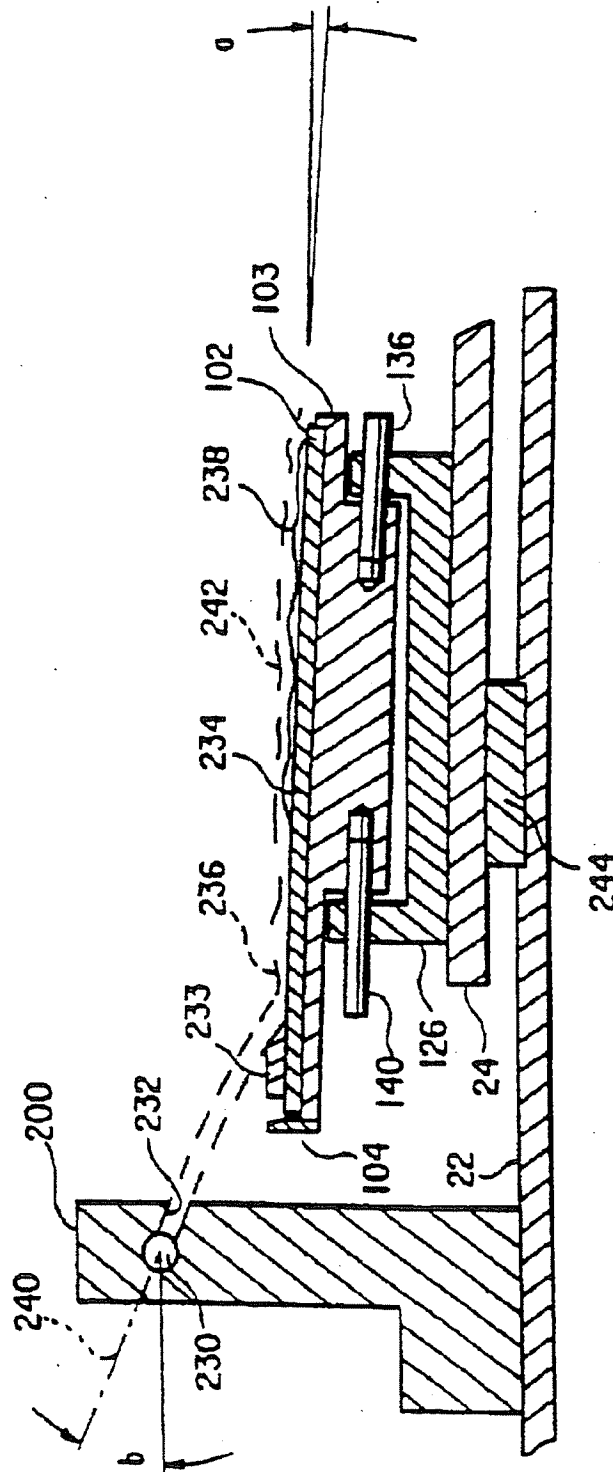


FIG. 12

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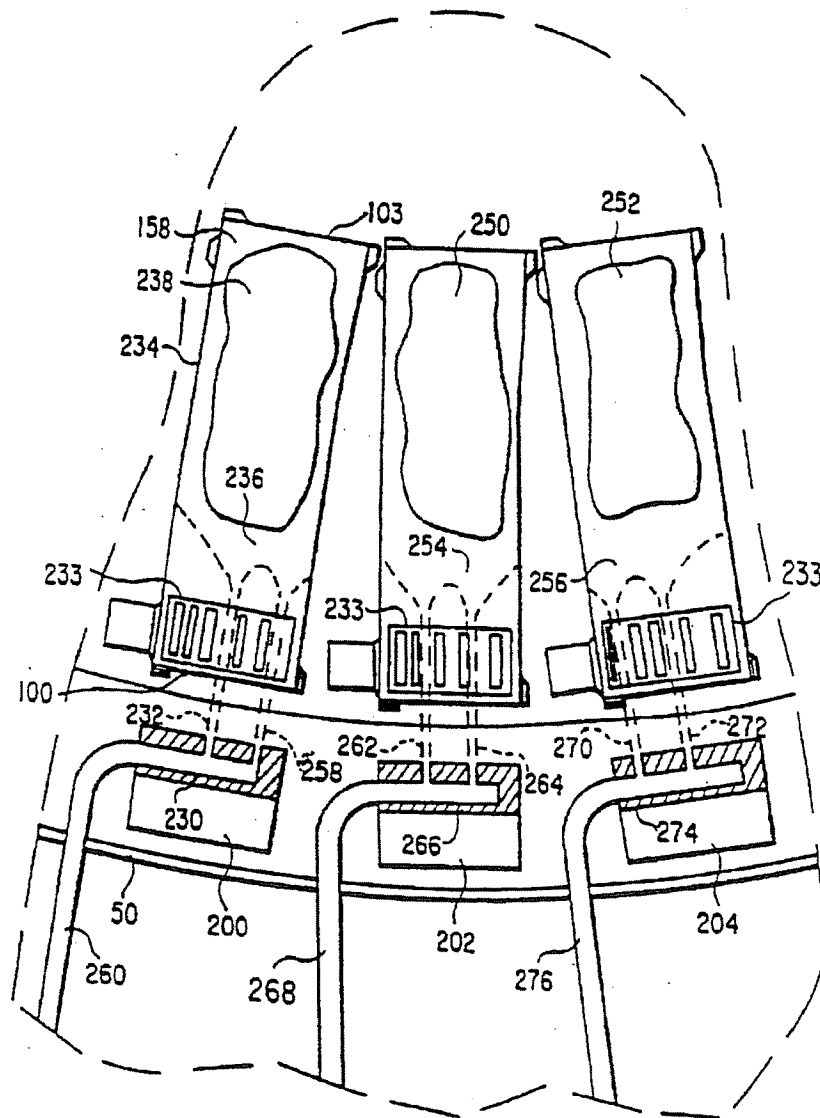


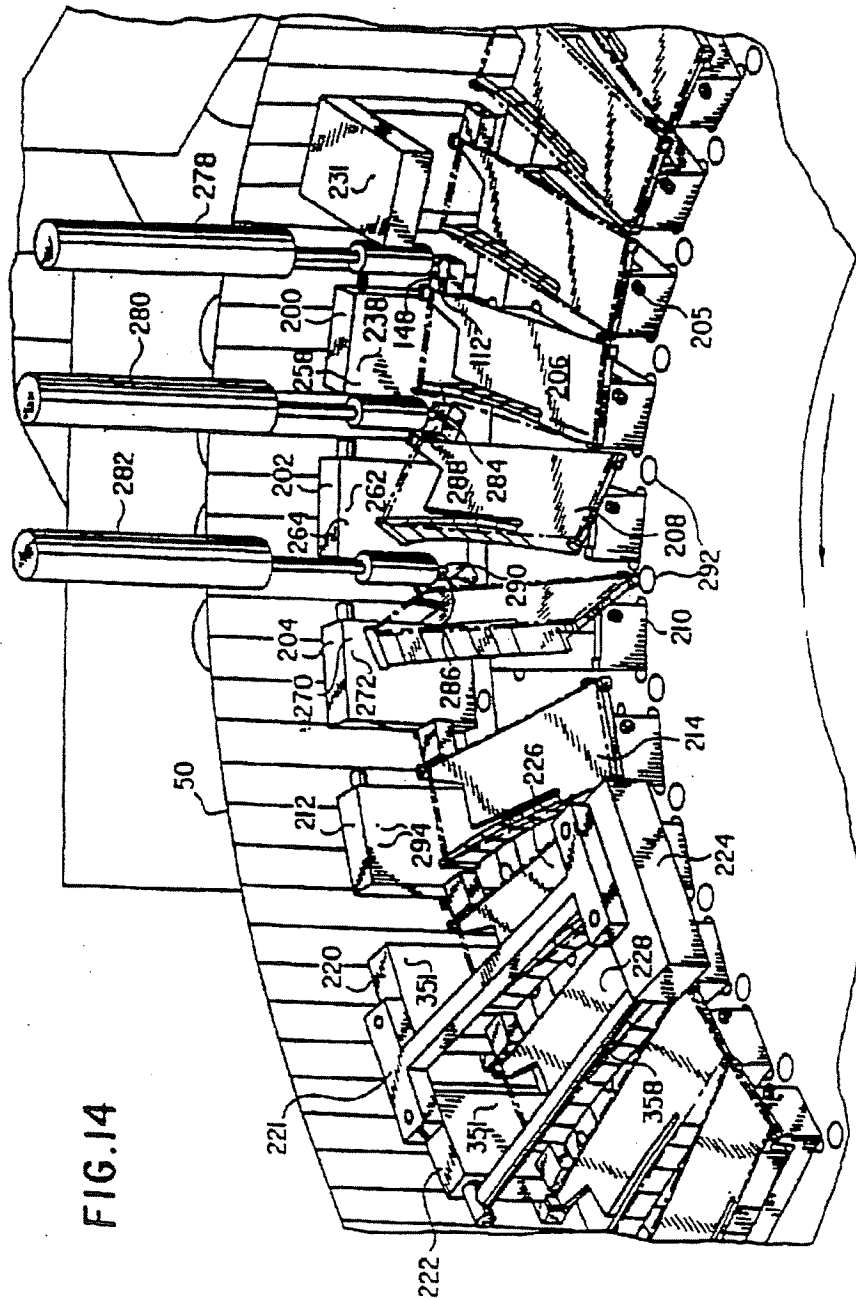
FIG. 13

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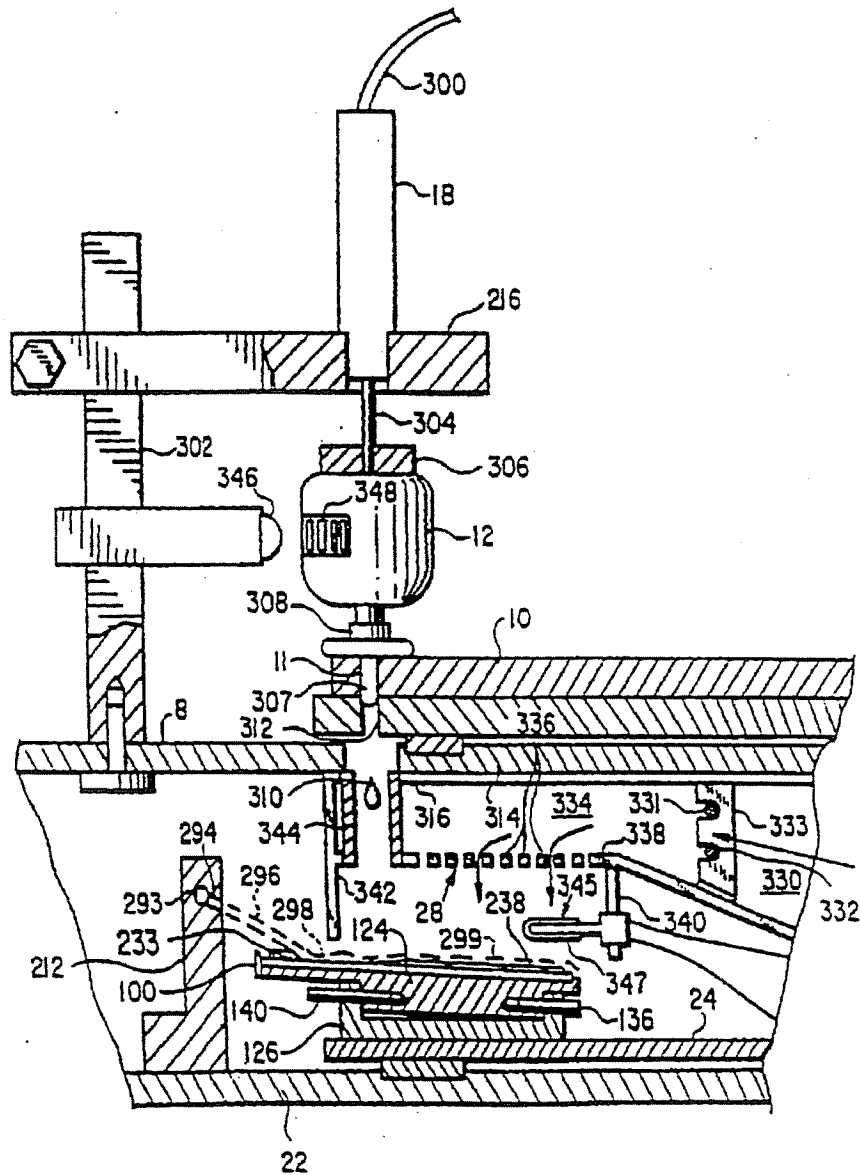


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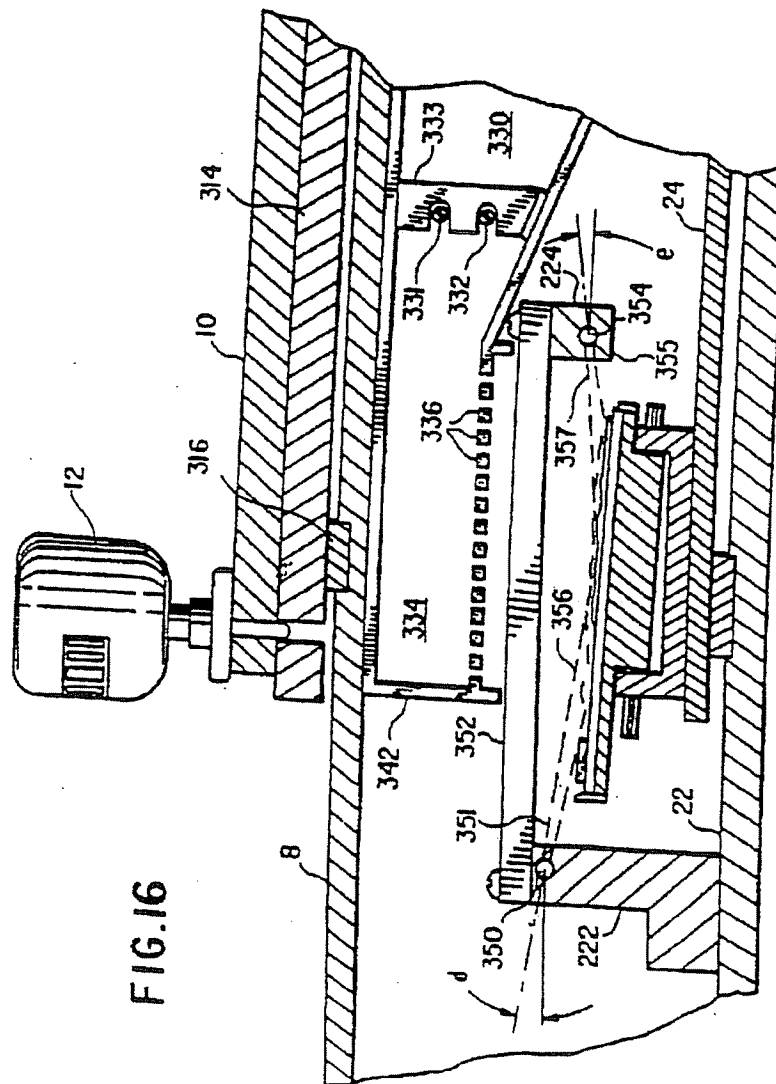


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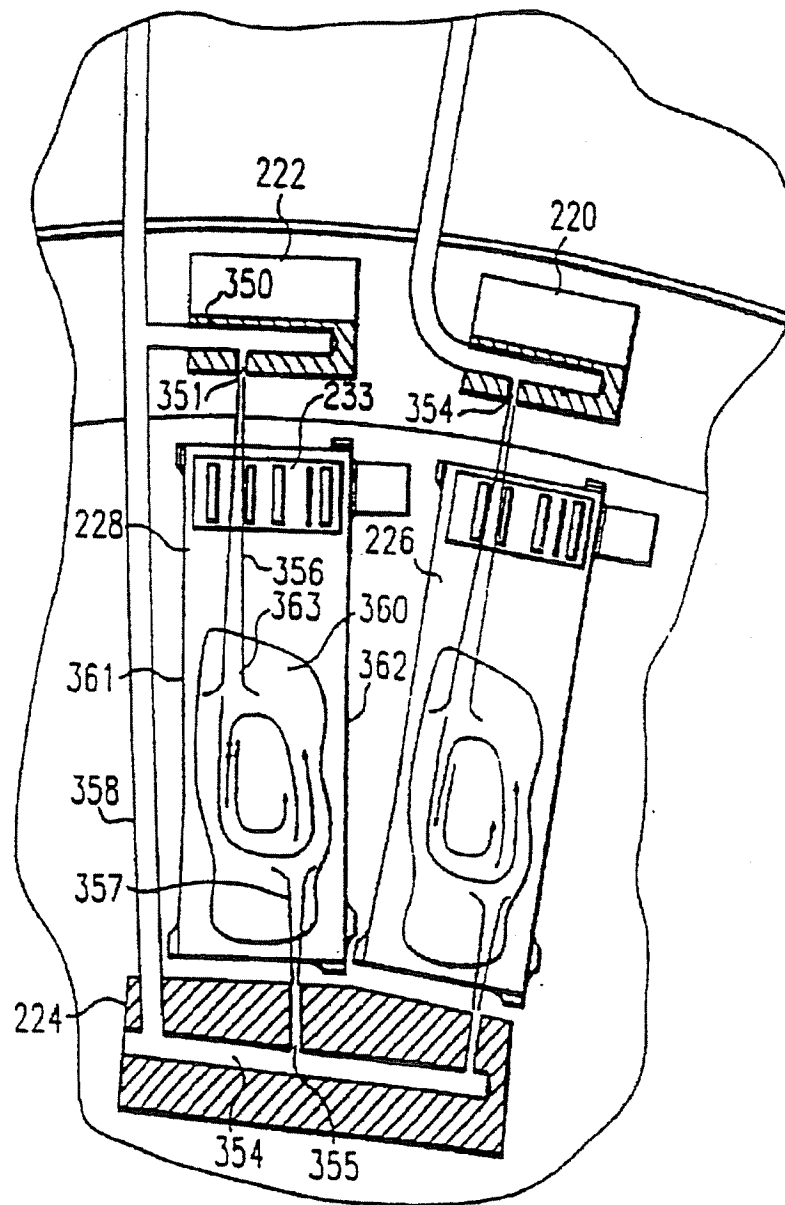


FIG. 17

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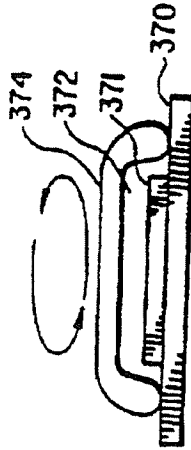


FIG. 18C

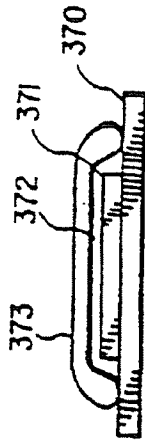


FIG. 18B

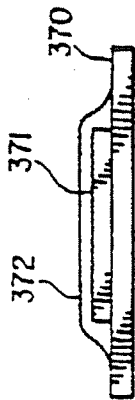


FIG. 18A

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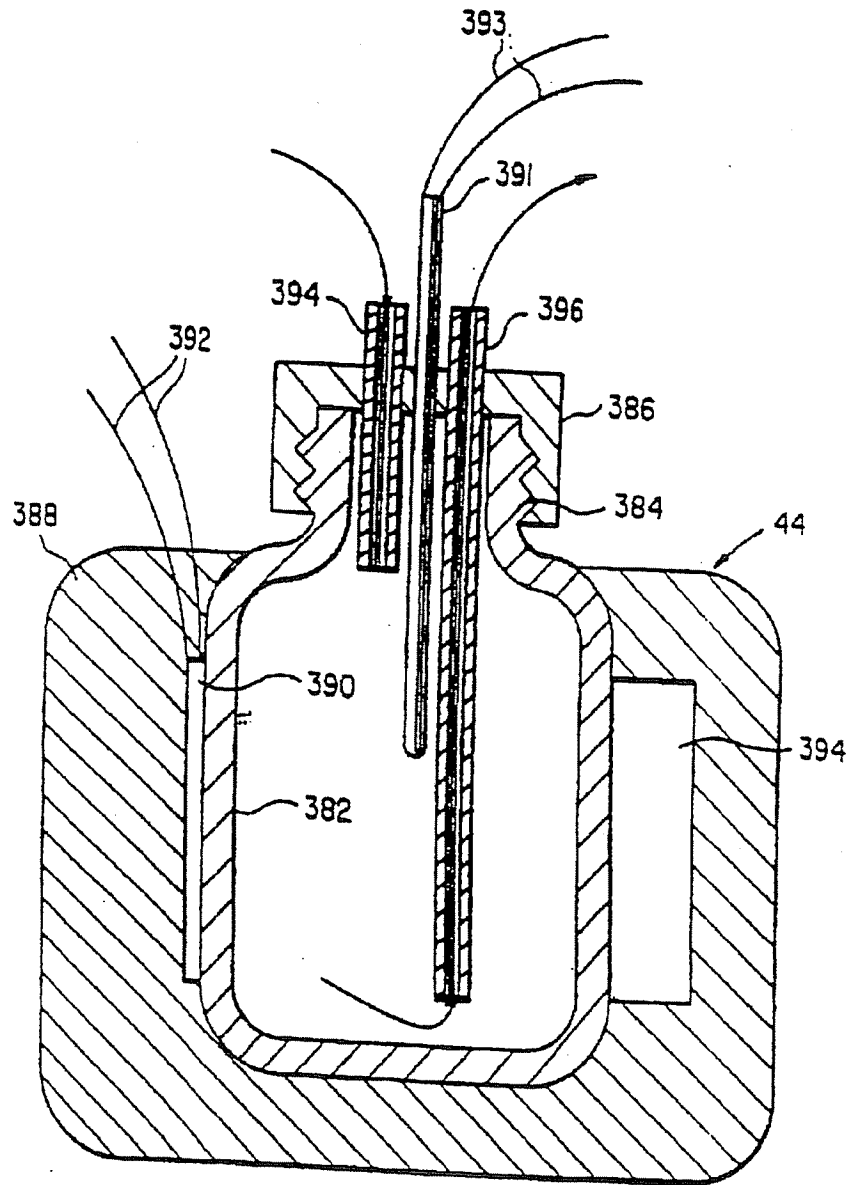


FIG. 19A

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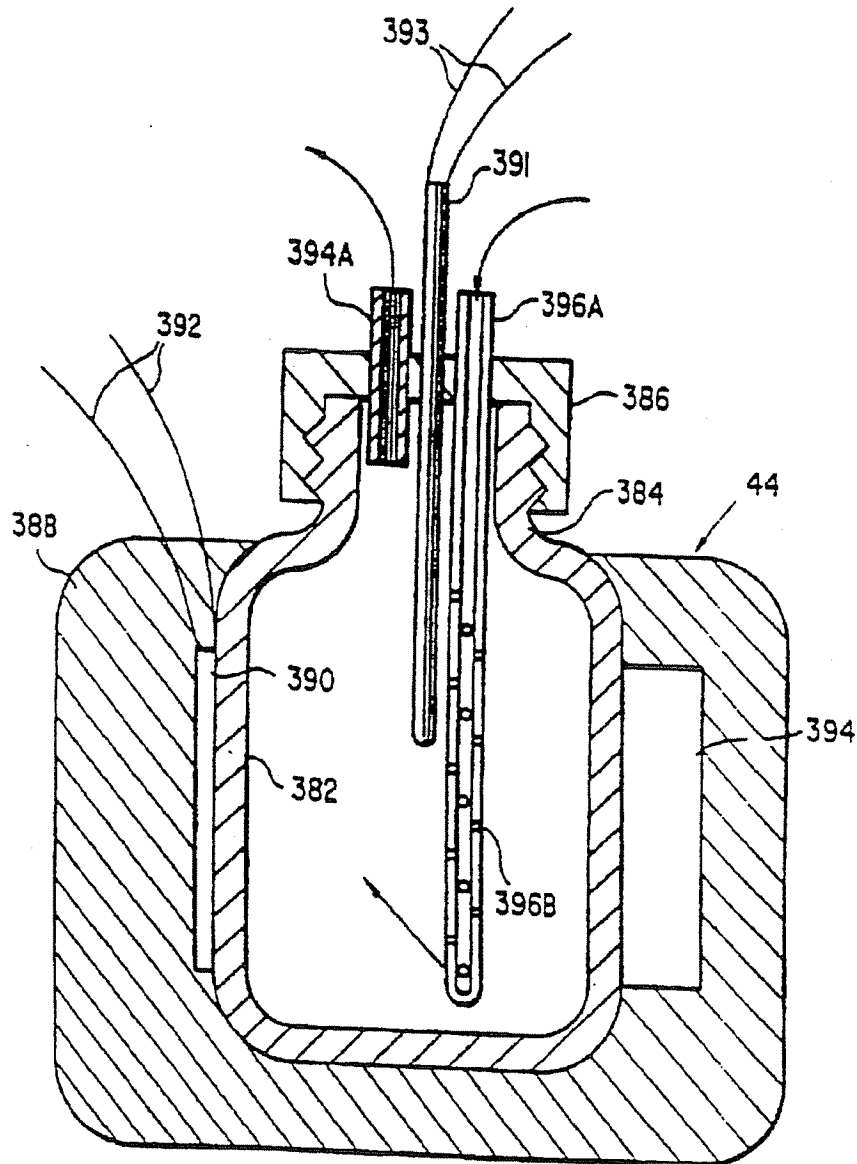


FIG.19B

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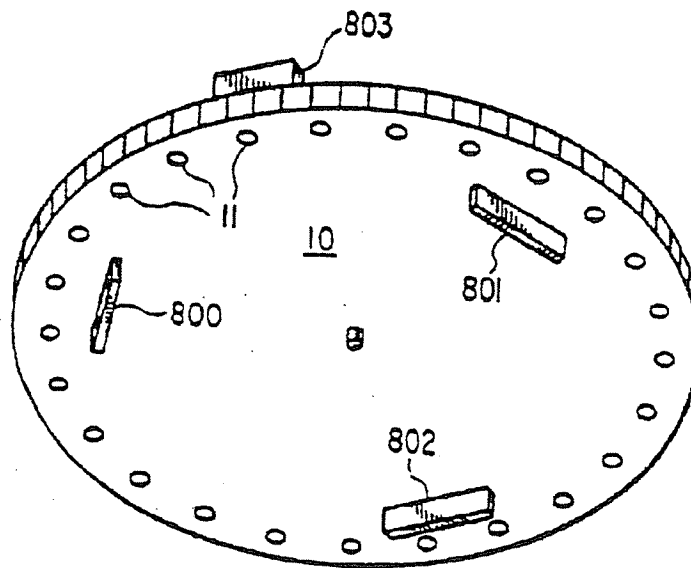


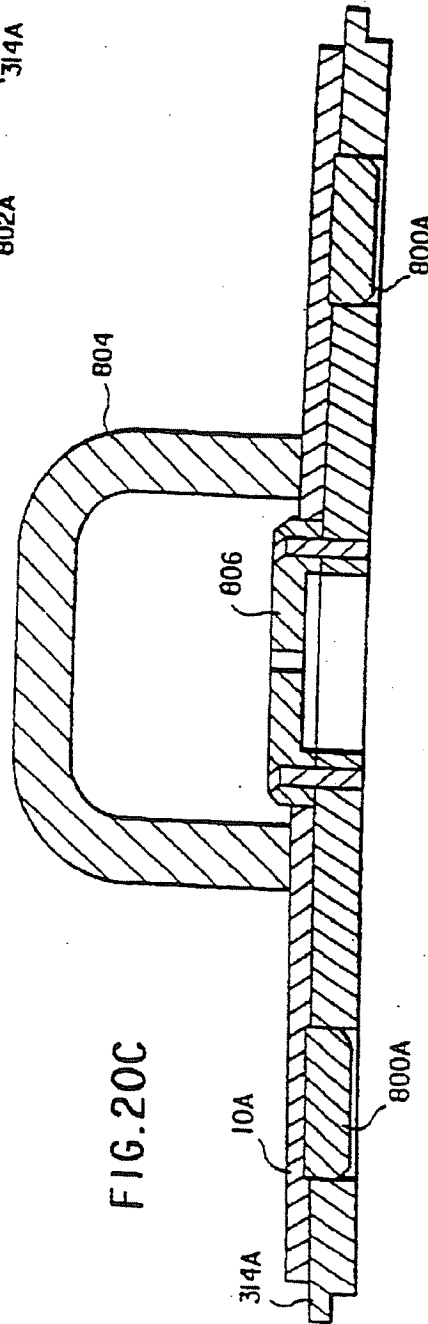
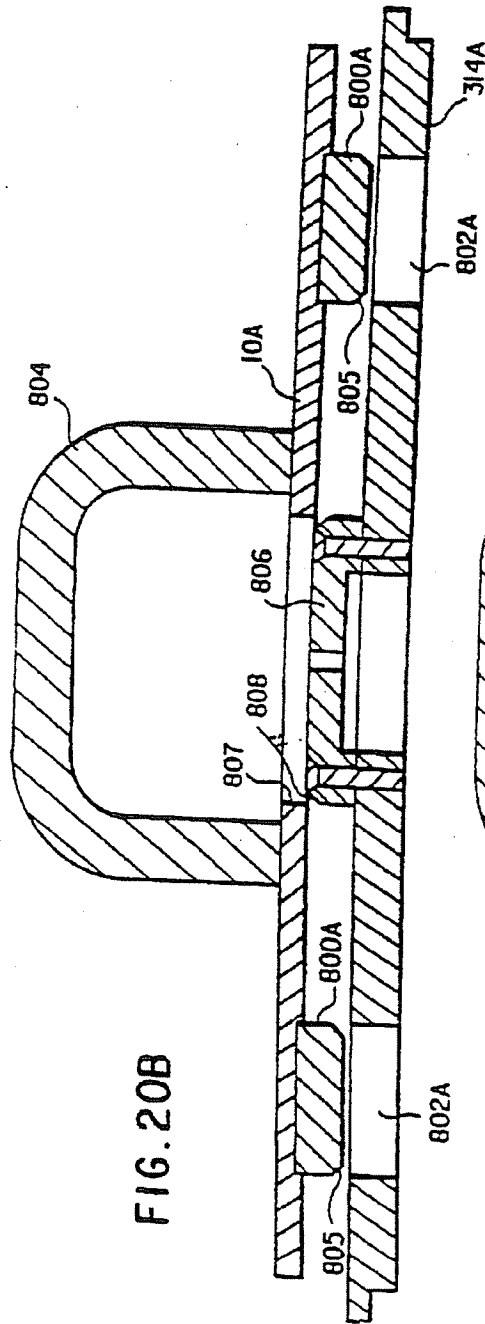
FIG. 20A

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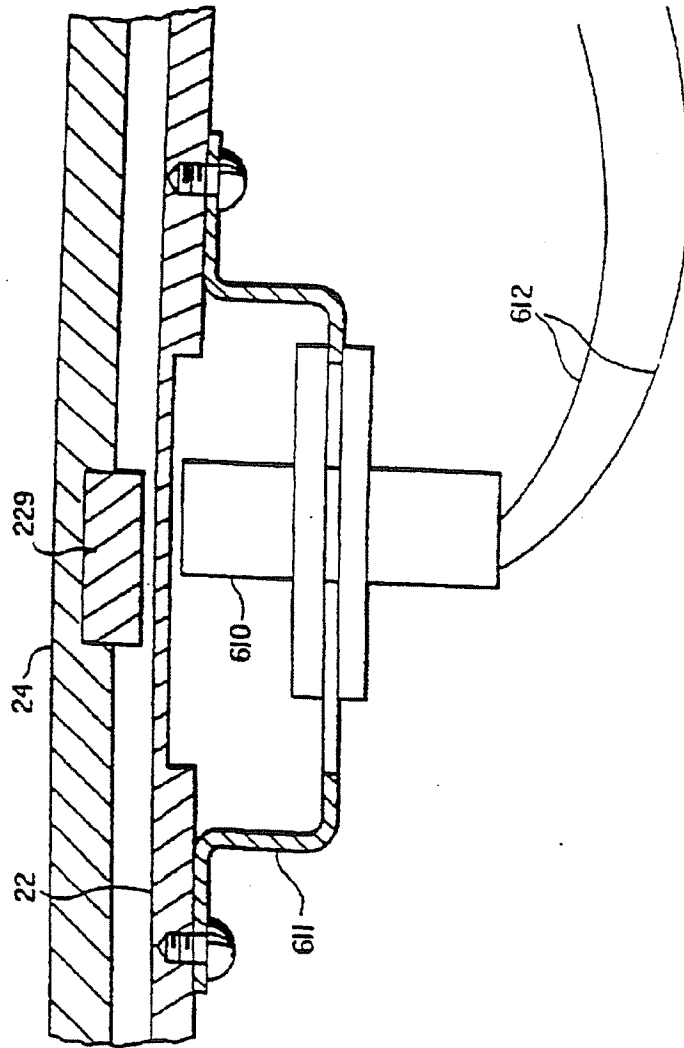
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FIG. 21



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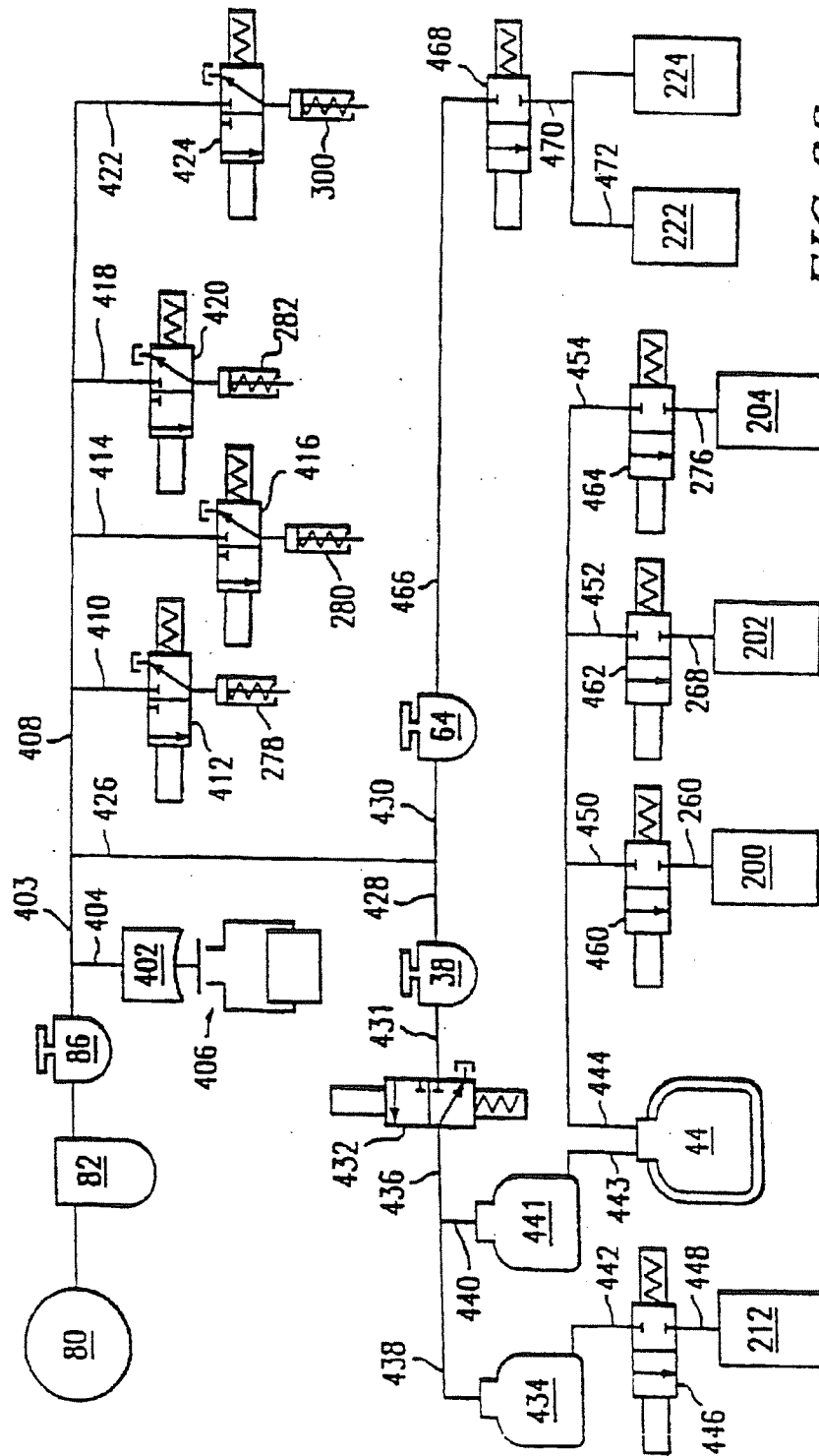


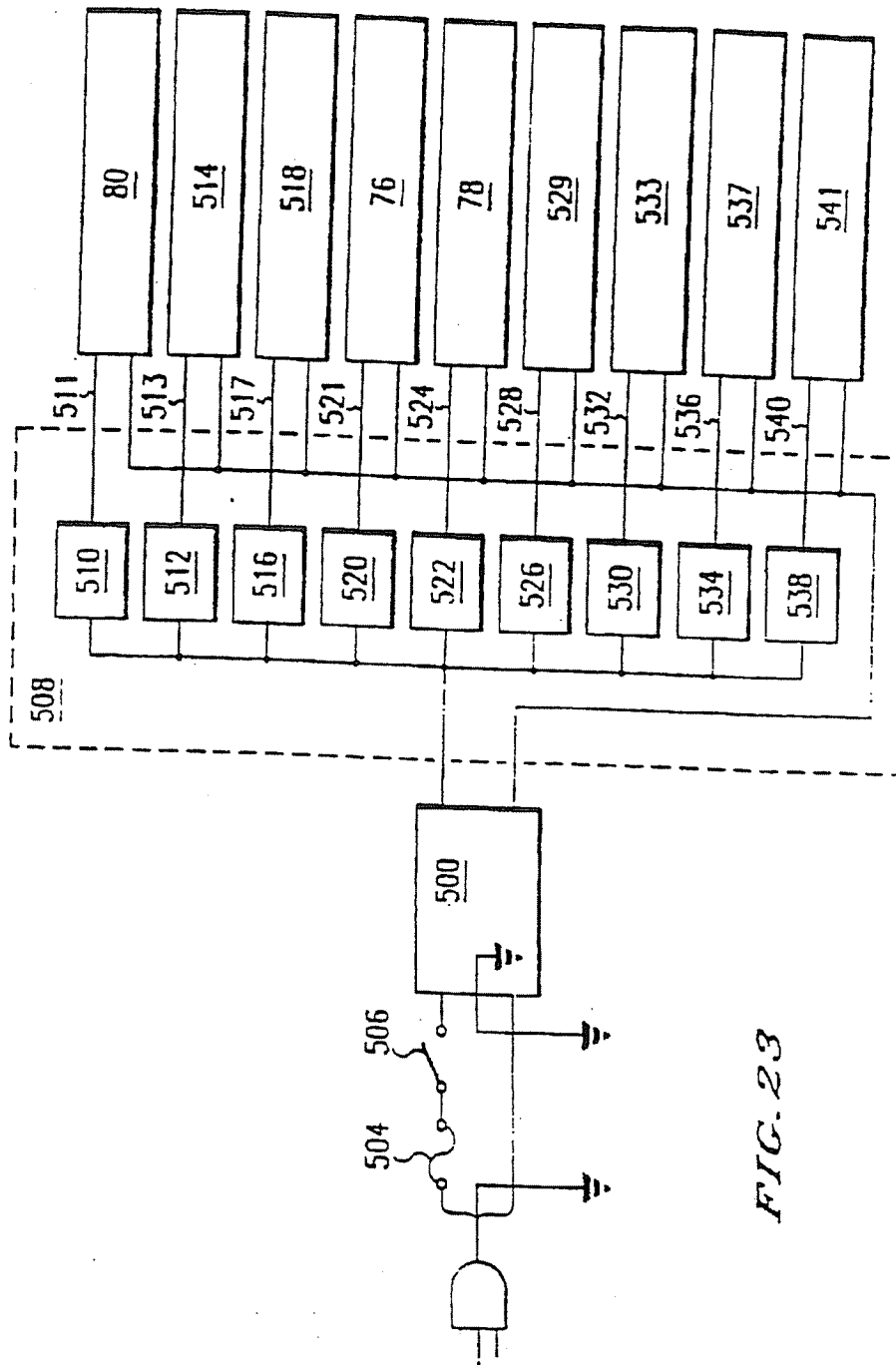
FIG. 22

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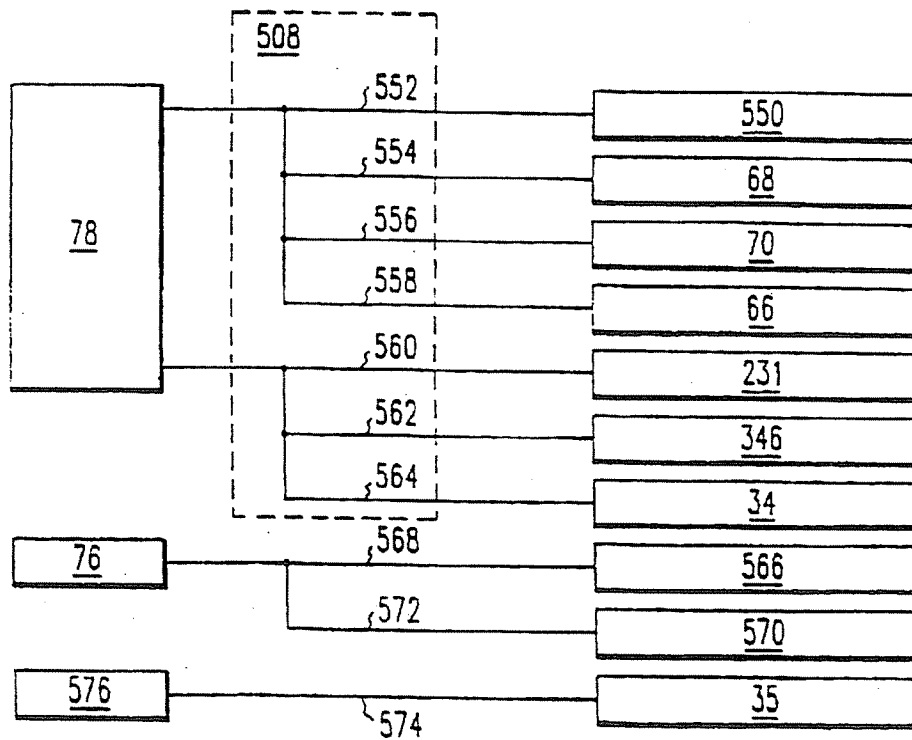


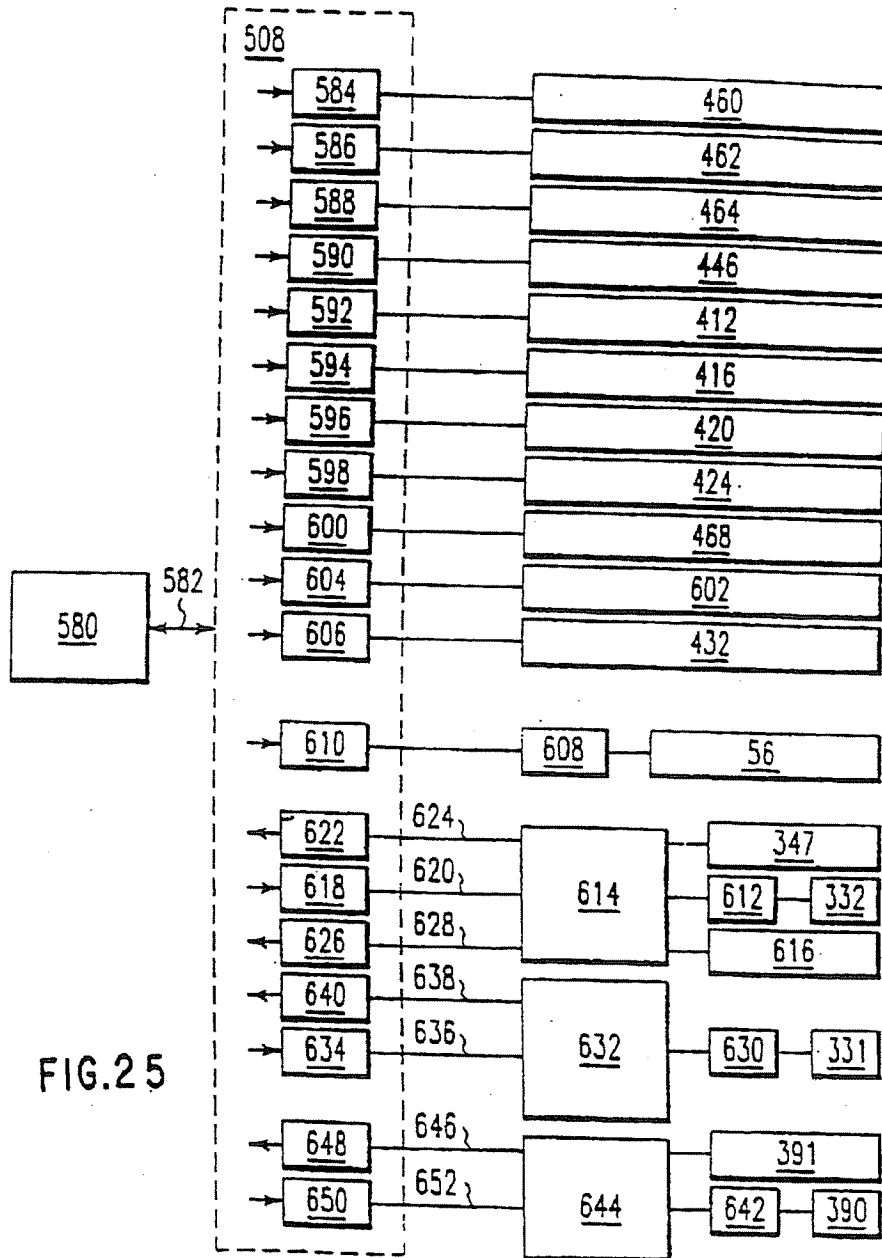
FIG. 24

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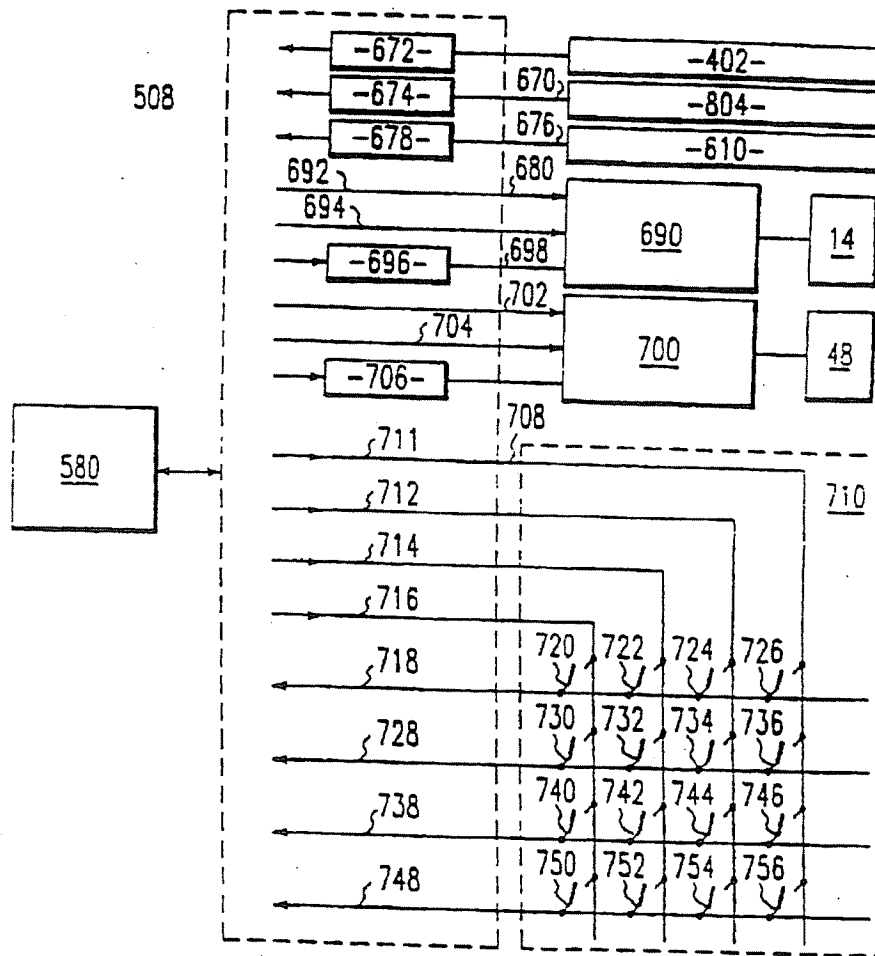


FIG. 26

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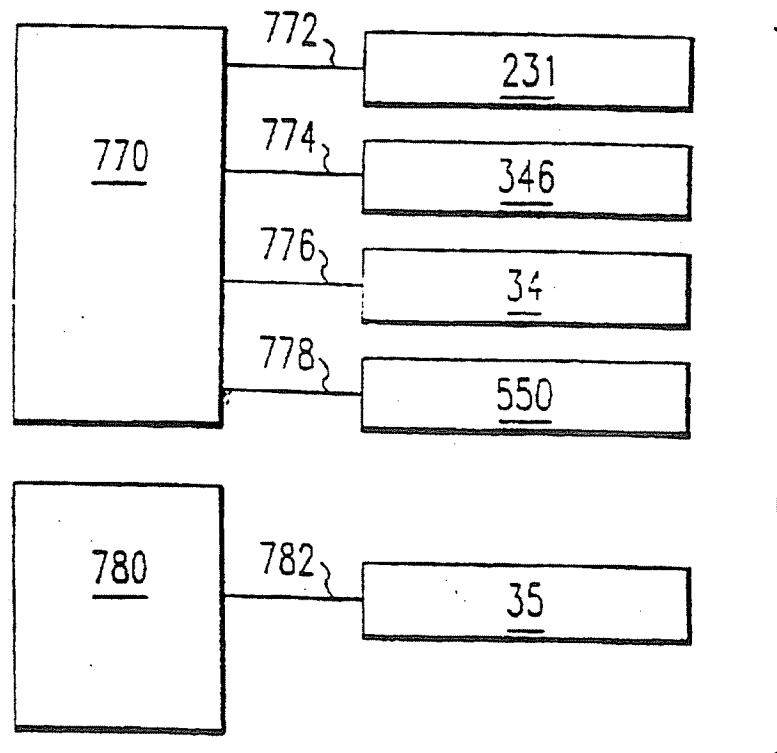


FIG. 27

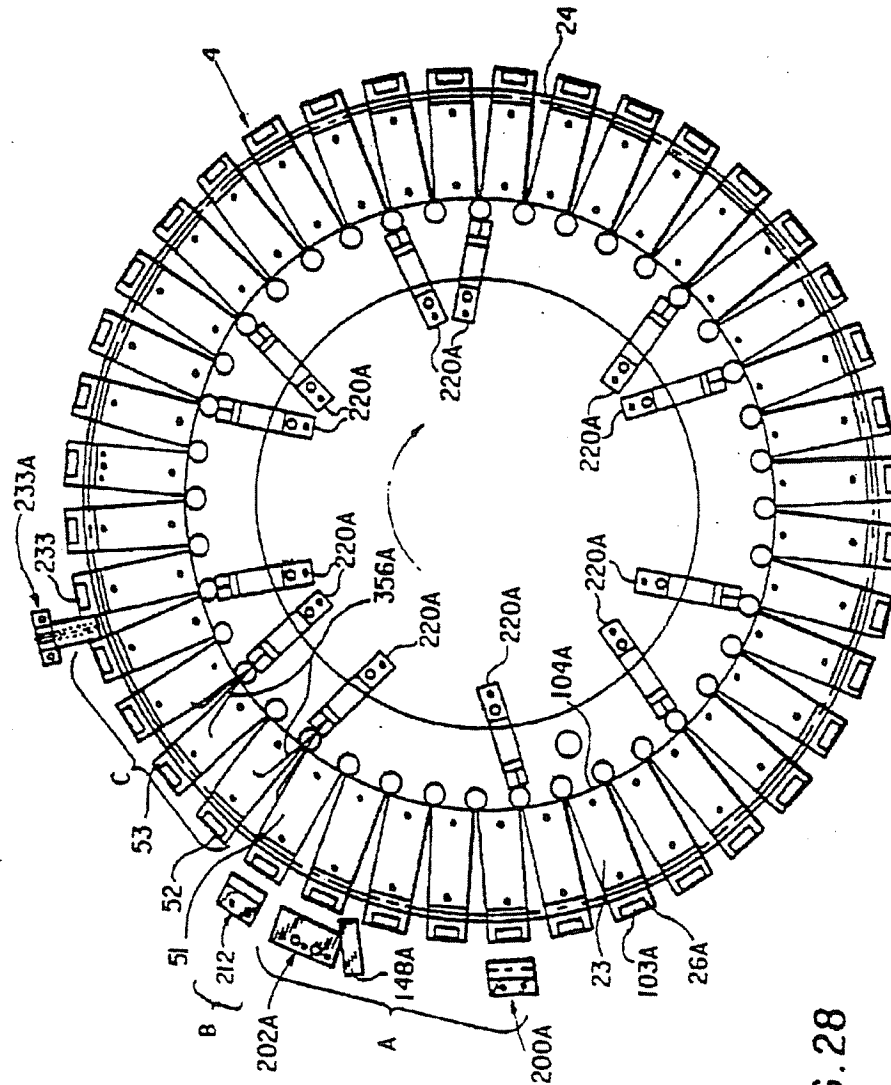


FIG. 28

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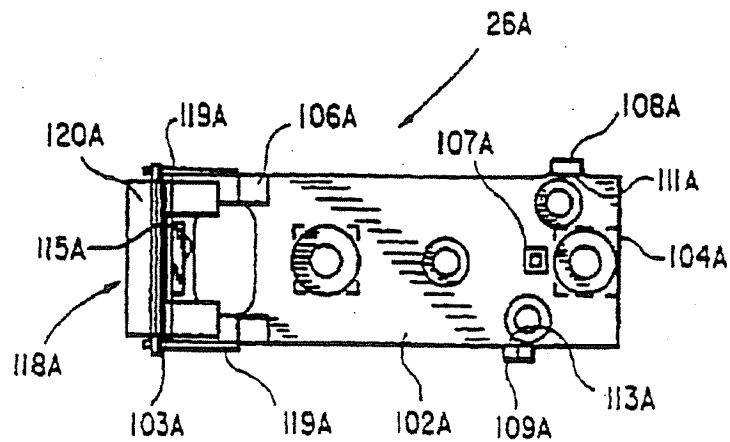


FIG. 29A

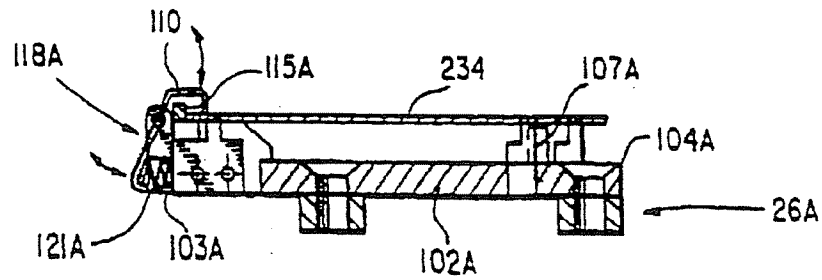


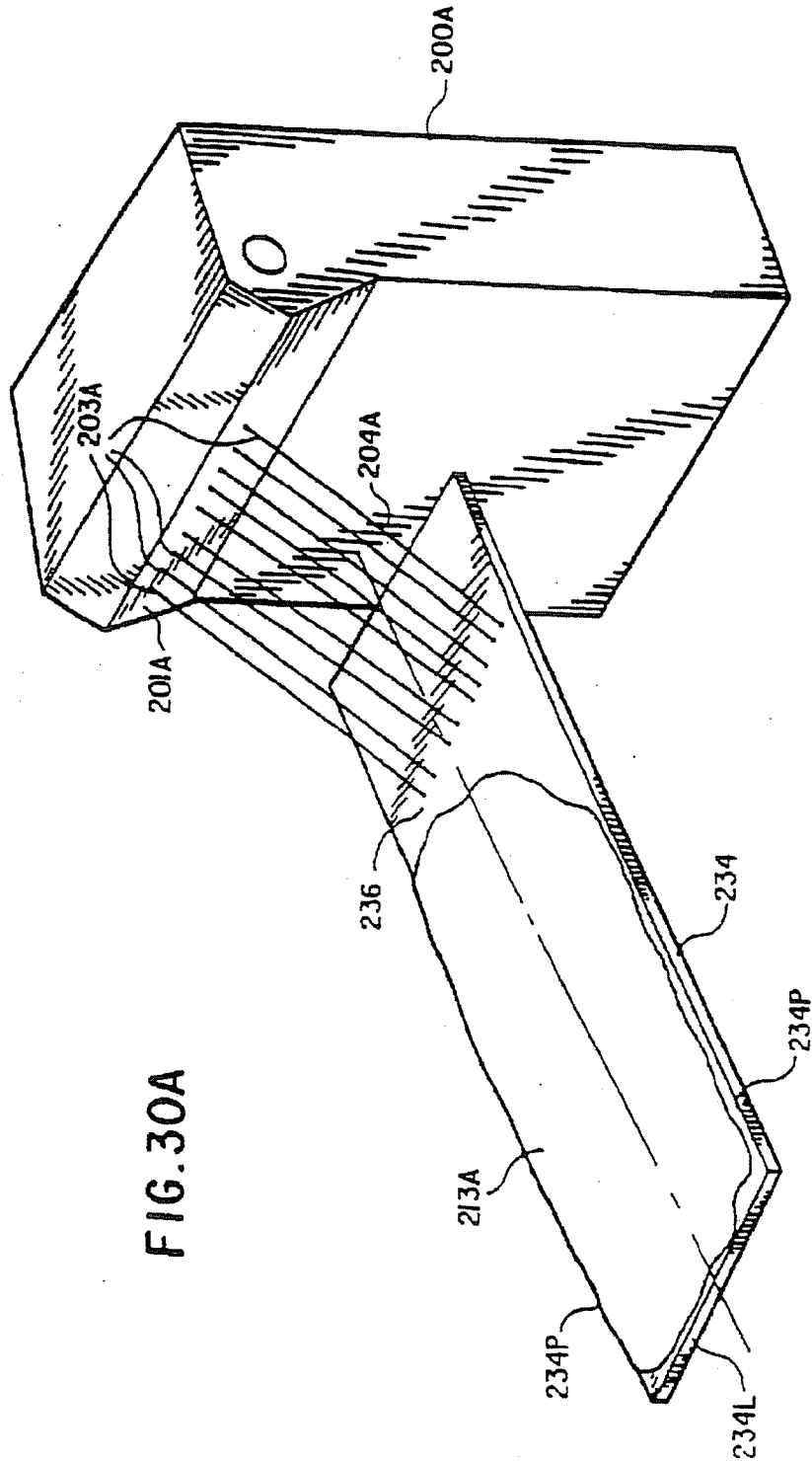
FIG. 29B

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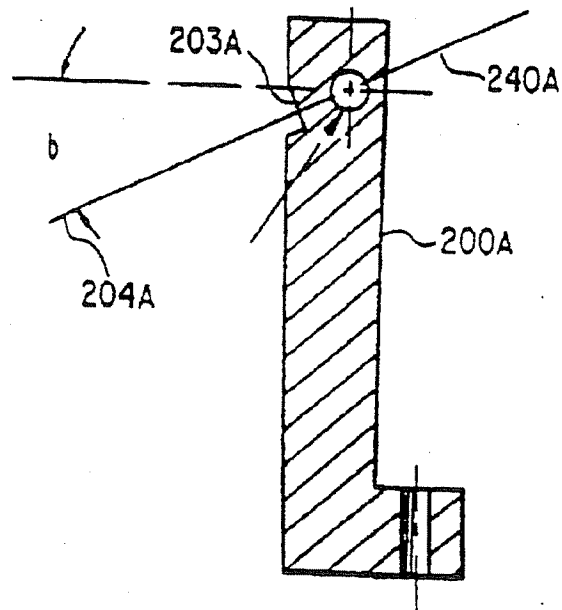


FIG. 30B